

Supplemental Preliminary Amendment
U.S. Patent Application No. 10/582,054

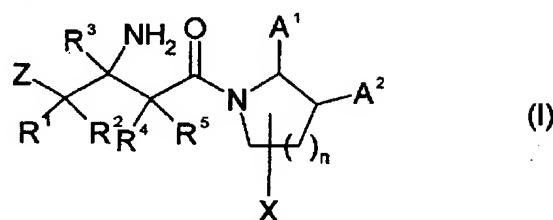
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Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Original) A compound of formula (I)



or a pharmaceutically acceptable salt thereof, wherein

Z is selected from the group consisting of

phenyl;

naphthyl;

C₃₋₇ cycloalkyl;

heterocycle; and

heterobicycle;

wherein Z is optionally substituted with one, or independently from each other, more of

halogen;

CN;

OH;

=O, where the ring is at least partially saturated;

C₁₋₆ alkyl, optionally substituted with one or more F; and

O-C₁₋₆ alkyl, optionally substituted with one or more F;

R¹, R², R⁴, R⁵ are independently from each other selected from the group consisting of

H;

F;

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OH;

C_{1-6} alkyl, optionally substituted with one or more F; and

$O-C_{1-6}$ alkyl, optionally substituted with one or more F;

and/or R^1 and R^2 optionally form together C_{3-7} cycloalkyl, which is optionally substituted with one or more F;

and/or R^2 and R^3 optionally form together C_{3-7} cycloalkyl, which is optionally substituted with one or more F;

and/or R^3 and R^4 optionally form together C_{3-7} cycloalkyl, which is optionally substituted with one or more F;

and/or R^4 and R^5 optionally form together C_{3-7} cycloalkyl, which is optionally substituted with one or more F;

R^3 is H or C_{1-6} alkyl;

X is selected from the group consisting of

H;

F; and

C_{1-6} alkyl, optionally substituted with one or more F;

n is 0, 1 or 2;

A^1 , A^2 are independently from each other selected from the group consisting of H;

halogen;

C_{1-6} alkyl, optionally substituted with one or more F; and

R^6 ; provided that one of A^1 and A^2 is R^6 ;

R^6 is $-C(R^7R^8)-Y-T$;

R^7 , R^8 are independently from each other selected from the group consisting of H;

F; and

C_{1-6} alkyl, optionally substituted with one or more F;

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and/or R⁷ and R⁸ optionally form together C₃₋₇ cycloalkyl, which is optionally substituted with one or more F;

Y is selected from the group consisting of

- O-;
- C₁₋₆ alkyl-O-;
- N(R⁹)-;
- C₁₋₆ alkyl-N(R⁹)-;
- S-;
- C₁₋₆ alkyl-S-;
- S(O)-;
- C₁₋₆ alkyl-S(O)-;
- S(O)₂-; and
- C₁₋₆ alkyl-S(O)₂-;

wherein each C₁₋₆ alkyl is optionally substituted with one or more F;

R⁹, T are independently from each other T¹-T² or T²,

T¹ is selected from the group consisting of

- C₁₋₆ alkyl-;
- C₁₋₆ alkyl-O-;
- C₁₋₆ alkyl-N(R¹⁰)-;
- C(O)-;
- C(O)-C₁₋₆ alkyl-;
- C(O)-C₁₋₆ alkyl-O-;
- C(O)-C₁₋₆ alkyl-N(R¹⁰)-;
- C(O)O-;
- C(O)O-C₁₋₆ alkyl-;
- C(O)O-C₁₋₆ alkyl-O-;
- C(O)O-C₁₋₆ alkyl-N(R¹⁰)-;
- C(O)N(R¹⁰)-;
- C(O)N(R¹⁰)-C₁₋₆ alkyl-;
- C(O)N(R¹⁰)-C₁₋₆ alkyl-O-;

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-C(O)N(R¹⁰)-C₁₋₆ alkyl-N(R¹¹)-;

-S(O)₂-;

-S(O)₂-C₁₋₆ alkyl-;

-S(O)₂-C₁₋₆ alkyl-O-; and

-S(O)₂-C₁₋₆ alkyl-N(R¹⁰)-;

wherein each C₁₋₆ alkyl is optionally substituted with one or more F;

R¹⁰, R¹¹ are independently from each other H or C₁₋₆ alkyl, optionally substituted with one or more F;

T² is selected from the group consisting of

H;

CF₃;

phenyl;

naphthyl;

wherein phenyl and naphthyl are optionally substituted with one, or independently from each other, more of

halogen;

CN;

R¹²;

COOH;

OH;

C(O)NH₂;

S(O)₂NH₂;

COOT³;

OT³;

C(O)NHT³;

S(O)₂NHT³; or

T³;

C₃₋₇ cycloalkyl;

heterocycle; and

heterobicycle;

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wherein C₃₋₇ cycloalkyl, heterocycle and heterobicycle are optionally substituted with one, or independently from each other, more of halogen;

CN;

R¹³;

OH;

=O, where the ring is at least partially saturated;

NH₂

COOH;

C(O)NH₂;

S(O)₂NH₂;

COOT³;

OT³;

C(O)NHT³;

S(O)₂NHT³;

NHT³; or

T³;

whereby when R⁹ is T¹-T² and represents -C₁₋₆ alkyl and T is T¹-T² and represents -C₁₋₆ alkyl then R⁹ and T may form together a 3 to 7 membered cyclic group containing 1 N;

R¹² is selected from the group consisting of

C₁₋₆ alkyl;

O-C₁₋₆ alkyl;

COO-C₁₋₆ alkyl;

OC(O)-C₁₋₆ alkyl;

C(O)N(R¹⁵)-C₁₋₆ alkyl;

S(O)₂N(R¹⁷)-C₁₋₆ alkyl;

S(O)-C₁₋₆ alkyl;

S(O)₂-C₁₋₆ alkyl; and

N(R¹⁸)S(O)₂-C₁₋₆ alkyl;

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wherein each C₁₋₆ alkyl is optionally substituted with one, or independently from each other, more of F, COOR¹⁹, C(O)N(R²⁰R²¹), S(O)₂N(R²²R²³), OR²⁴, N(R²⁵R²⁶), T³, O-T³ or N(R²⁷)-T³;

R¹³ is selected from the group consisting of

C₁₋₆ alkyl;

O-C₁₋₆ alkyl;

N(R¹⁴)-C₁₋₆ alkyl;

COO-C₁₋₆ alkyl;

OC(O)-C₁₋₆ alkyl;

C(O)N(R¹⁵)-C₁₋₆ alkyl;

N(R¹⁶)-C(O)-C₁₋₆ alkyl;

S(O)₂N(R¹⁷)-C₁₋₆ alkyl;

S(O)-C₁₋₆ alkyl;

S(O)₂-C₁₋₆ alkyl; and

-N(R¹⁸)S(O)₂-C₁₋₆ alkyl;

wherein each C₁₋₆ alkyl is optionally substituted with one, or independently from each other, more of F, COOR¹⁹, C(O)N(R²⁰R²¹), S(O)₂N(R²²R²³), OR²⁴, N(R²⁵R²⁶), T³, O-T³ or N(R²⁷)-T³;

R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷ are independently from each other H or C₁₋₆ alkyl;

T³ is selected from the group consisting of

phenyl;

naphthyl;

wherein phenyl and naphthyl are optionally substituted with one, or independently from each other, more of

halogen;

CN;

COOH;

OH;

C(O)NH₂;

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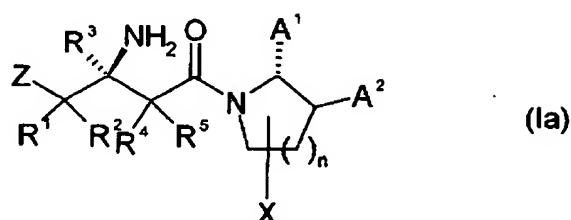
$\text{S(O)}_2\text{NH}_2$;
 C_{1-6} alkyl;
 O-C_{1-6} alkyl;
 COO-C_{1-6} alkyl;
 OC(O)-C_{1-6} alkyl;
 $\text{C(O)N(R}^{28}\text{)-C}_{1-6}$ alkyl;
 $\text{S(O)}_2\text{N(R}^{29}\text{)-C}_{1-6}$ alkyl;
 $\text{S(O)}_2\text{-C}_{1-6}$ alkyl; or
 $\text{N(R}^{30}\text{)S(O)}_2\text{-C}_{1-6}$ alkyl;
heterocycle;
heterobicycle; and
 C_{3-7} cycloalkyl;

wherein C_{3-7} cycloalkyl, heterocycle and heterobicycle are optionally substituted with one, or independently from each other, more of halogen;

CN ;
 OH ;
 $=\text{O}$, where the ring is at least partially saturated;
 NH_2
 COOH ;
 C(O)NH_2 ;
 $\text{S(O)}_2\text{NH}_2$;
 C_{1-6} alkyl;
 O-C_{1-6} alkyl;
 $\text{N(R}^{31}\text{)-C}_{1-6}$ alkyl;
 COO-C_{1-6} alkyl;
 OC(O)-C_{1-6} alkyl;
 $\text{C(O)N(R}^{32}\text{)-C}_{1-6}$ alkyl;
 $\text{N(R}^{33}\text{)-C(O)-C}_{1-6}$ alkyl;
 $\text{S(O)}_2\text{N(R}^{34}\text{)-C}_{1-6}$ alkyl;
 $\text{S(O)}_2\text{-C}_{1-6}$ alkyl; or
 $-\text{N(R}^{35}\text{)S(O)}_2\text{-C}_{1-6}$ alkyl.

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2. (Original) A compound according to claim 1 of formula (Ia)



or a pharmaceutically acceptable salt thereof, wherein Z, R¹-R⁵, A¹, A², n and X have the meaning as indicated in claim 1.

3. (Previously presented) A compound according to claim 1, wherein Z is phenyl or heterocycle and Z is optionally substituted independently from each other with up to 2 of Cl, F, CN, CH₃ or OCH₃.
4. (Previously presented) A compound according to claim 1, wherein R¹, R², R⁴, R⁵ are independently from each other selected from the group consisting of H, F, OH CH₃, OCH₃.
5. (Previously presented) A compound according to claim 1, wherein R³ is H.
6. (Previously presented) A compound according to claim 1, wherein X is H, F or CH₃.
7. (Previously presented) A compound according to claim 1, wherein n is 1.
8. (Previously presented) A compound according to claim 1, wherein A¹ is R⁶ and A² is H, F or CH₃.
9. (Previously presented) A compound according to claim 1, wherein R⁶ is -CH₂-Y-T.
10. (Previously presented) A compound according to claim 1, wherein Y is -O-, -N(R⁹)- or -S(O)₂-.

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11. (Previously presented) A compound according to claim 1, wherein R⁹ is selected from the group consisting of H, CH₃, COOH, COOCH₃, C(O)NH₂, C(O)N(CH₃)₂, and S(O)₂CH₃.

12. (Previously presented) A compound according to claim 1, wherein T is T¹-T² or T² and wherein T¹ is selected from the group consisting of

- CH₂-;
- C(O)-;
- C(O)-CH₂-;
- C(O)O-;
- C(O)O-CH₂-;
- C(O)NH-;
- C(O)NH-CH₂-;
- S(O)₂-; and
- S(O)₂-CH₂-.

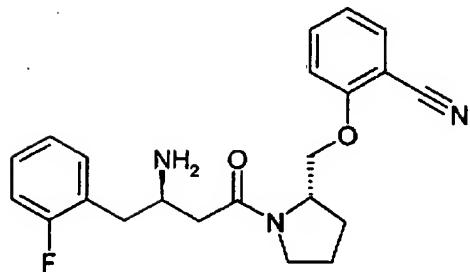
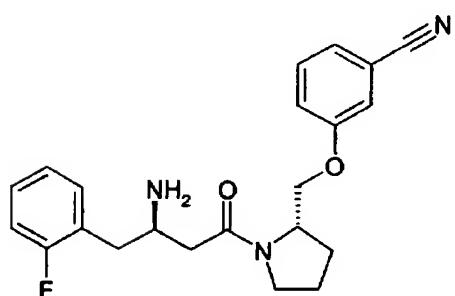
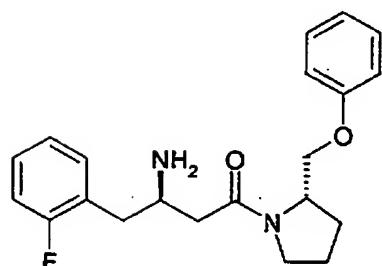
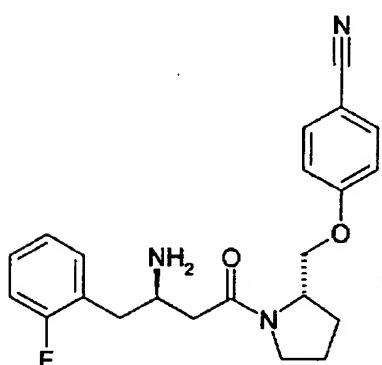
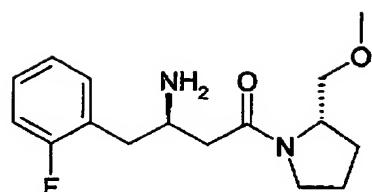
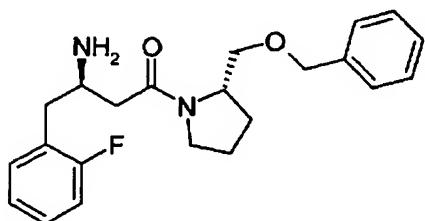
13. (Original) A compound according to claim 12, wherein T is T¹-T² or T² and wherein T¹ is selected from the group consisting of -C(O)-; -CH₂-; -S(O)₂-; and -C(O)NH-.

14. (Previously presented) A compound according to claim 1, wherein R⁸ is -CH₂-N(R³⁶)-T, and wherein R³⁶ is H or S(O)₂CH₃.

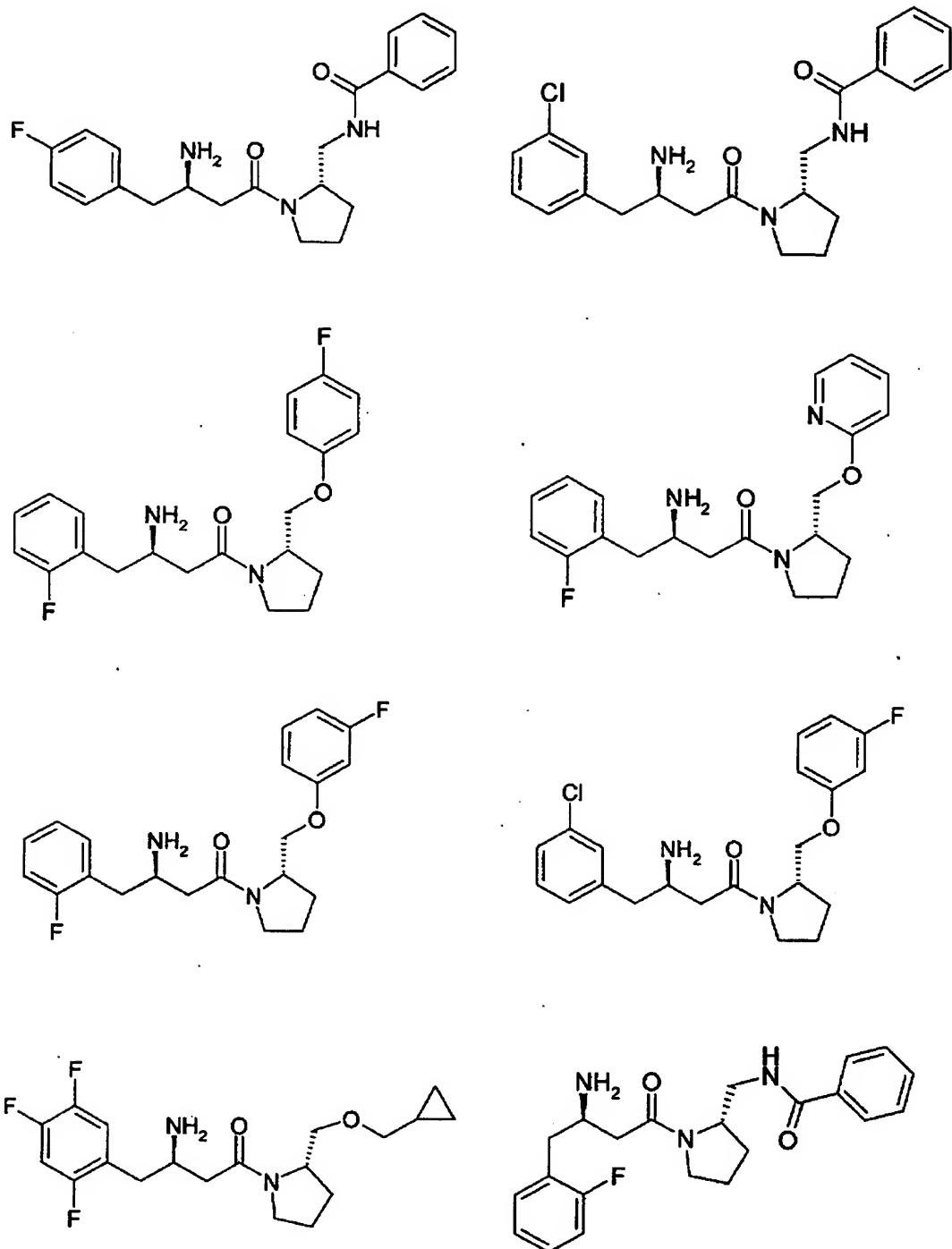
15. (Previously presented) A compound according to claim 1, wherein T² is phenyl or heterocycle.

16. (Original) A compound according to claim 1 selected from the group consisting of

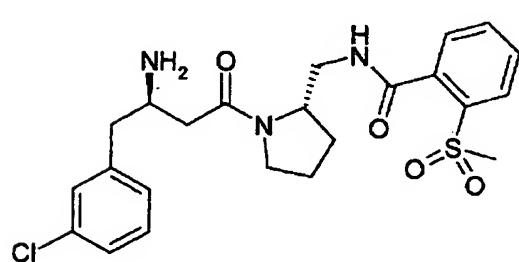
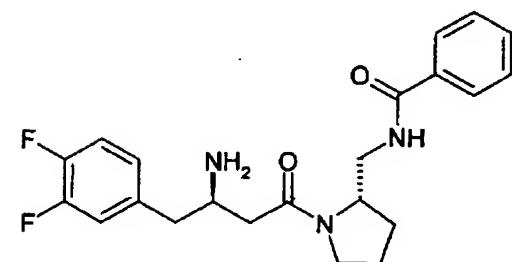
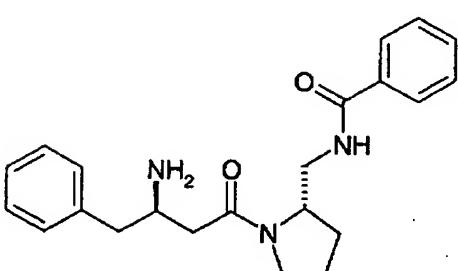
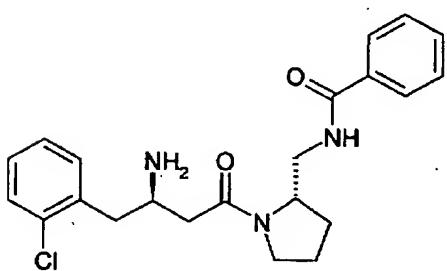
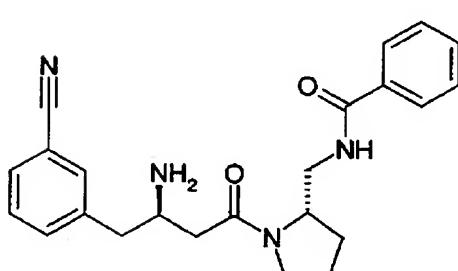
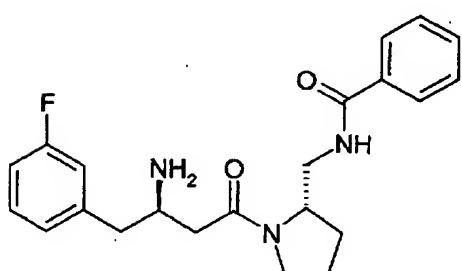
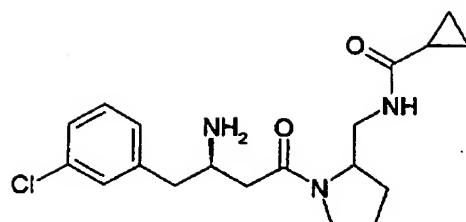
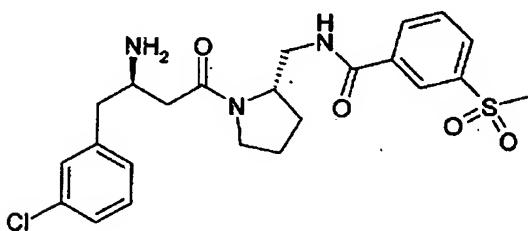
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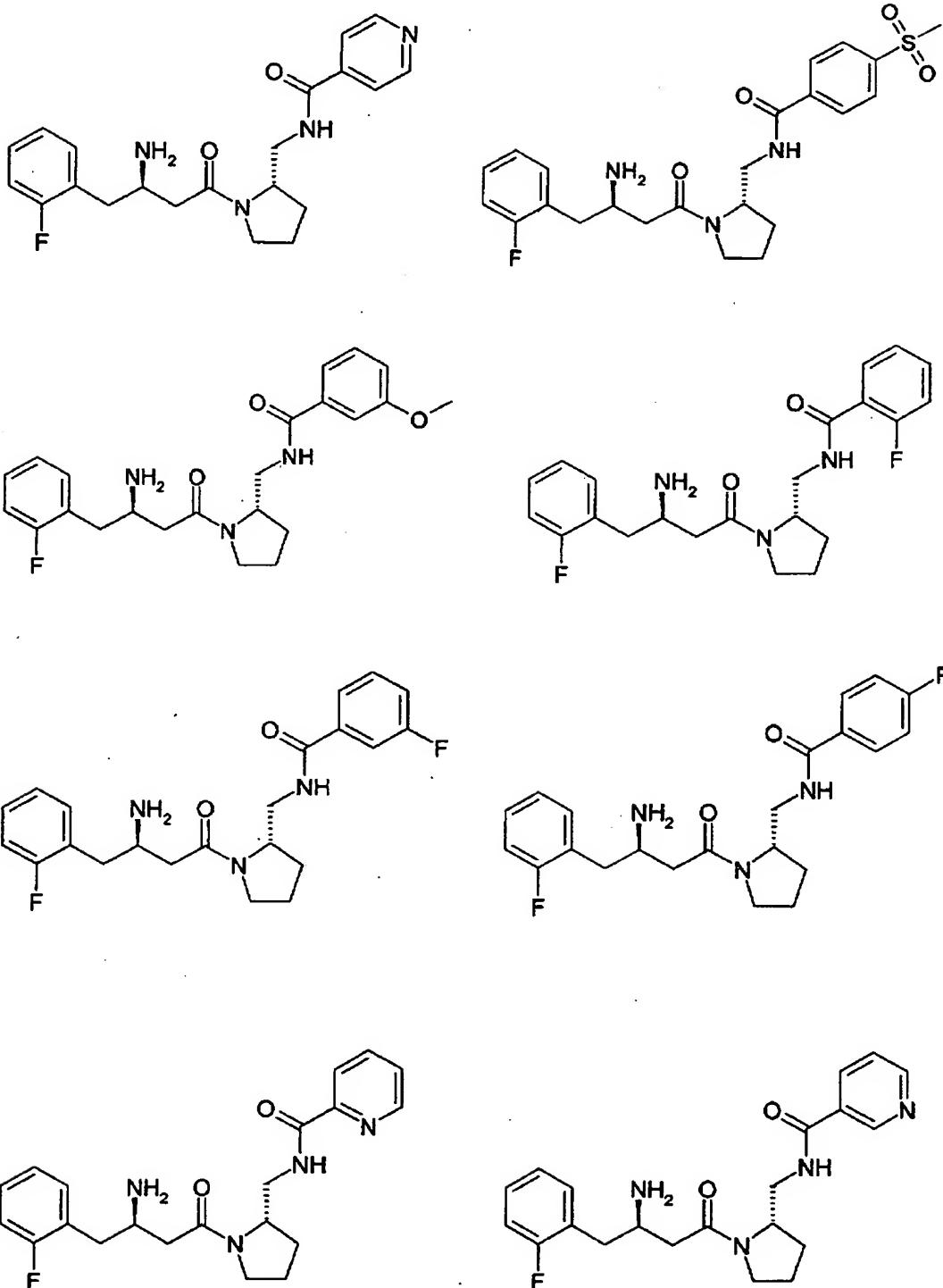
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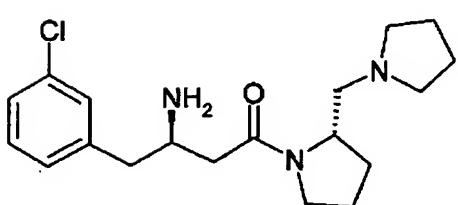
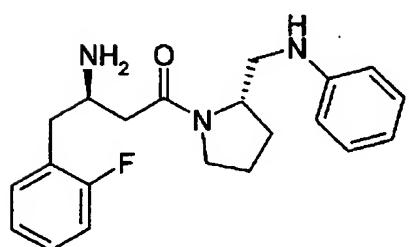
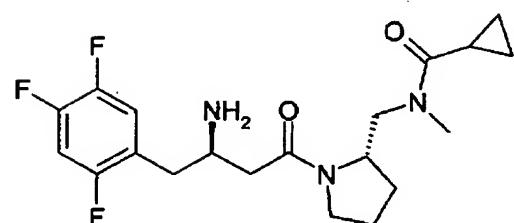
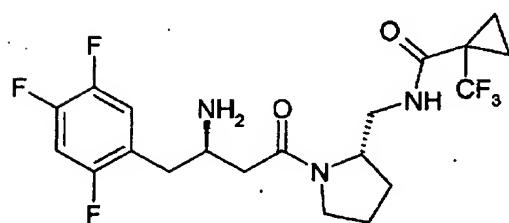
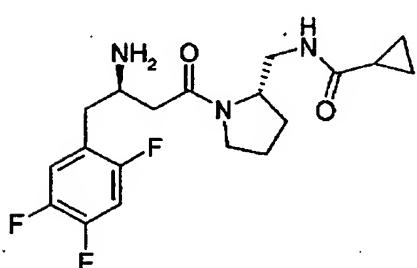
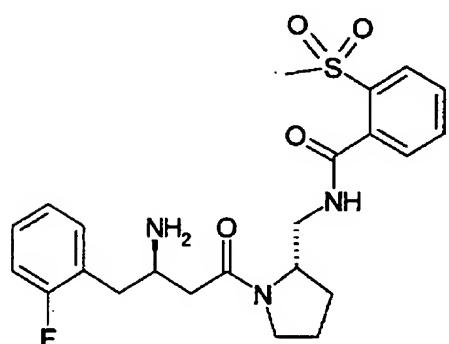
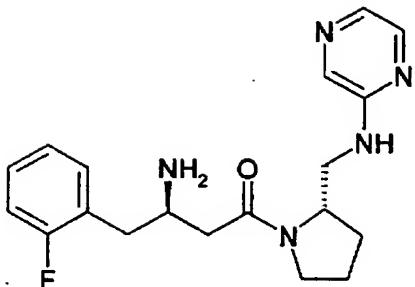
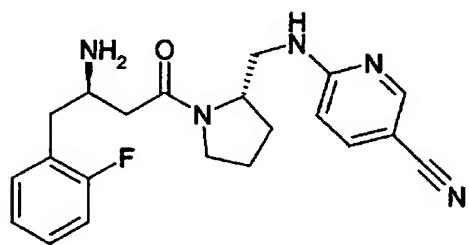
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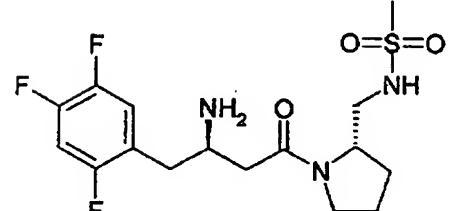
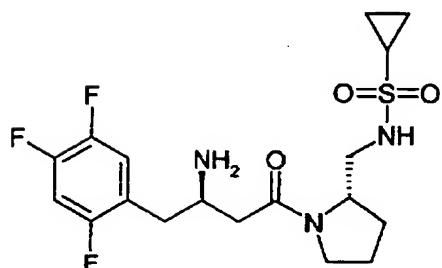
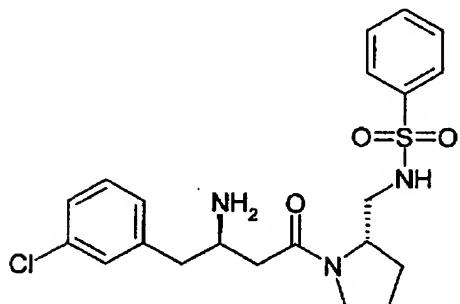
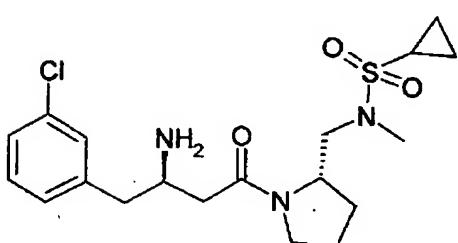
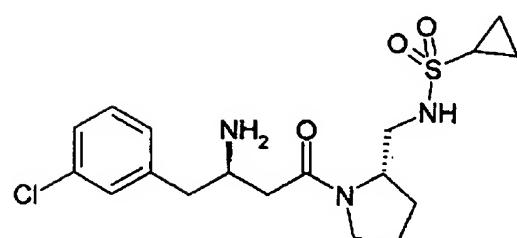
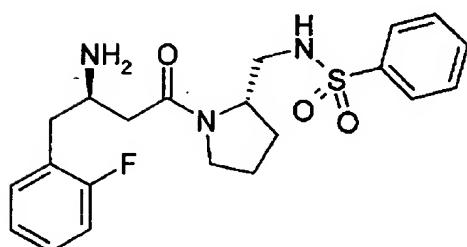
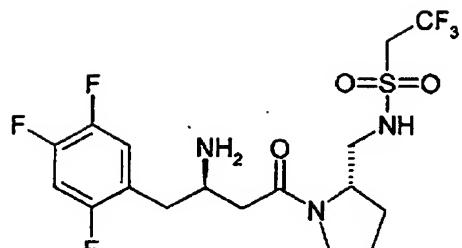
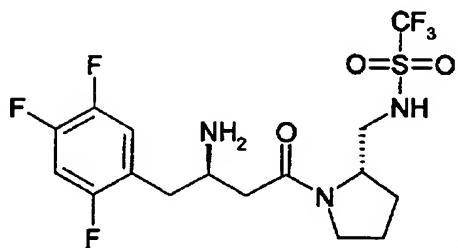
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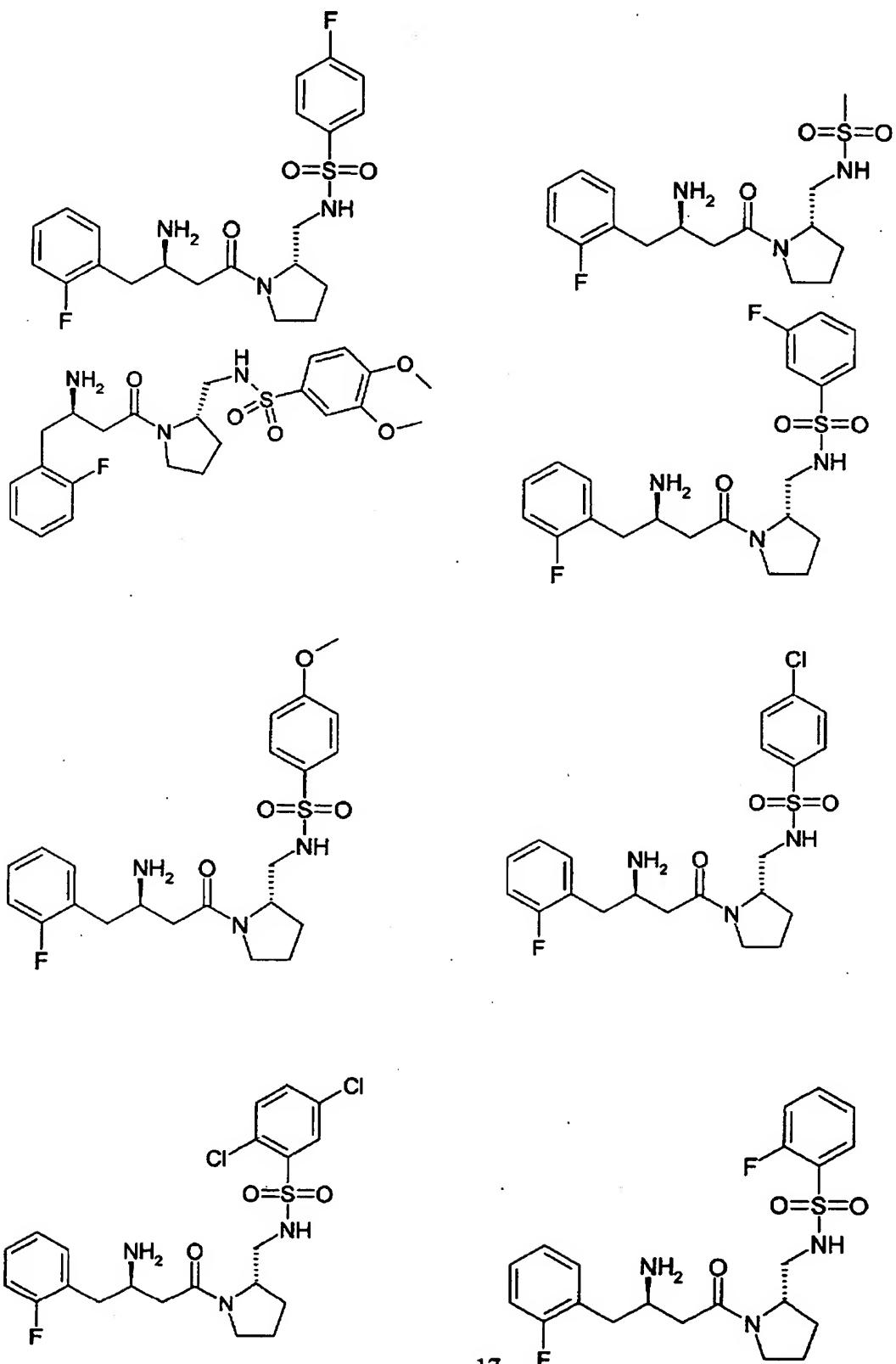
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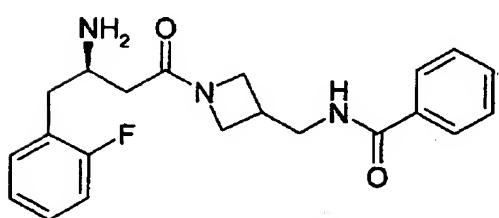
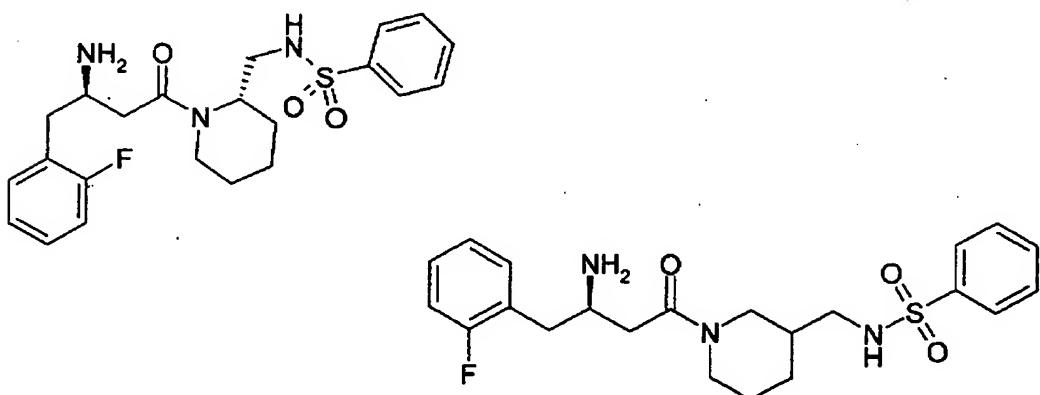
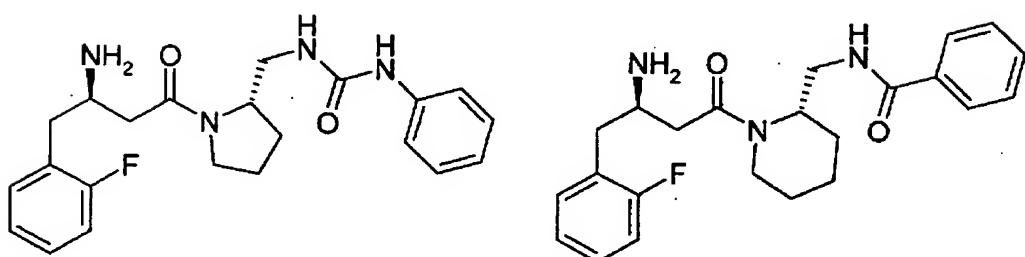
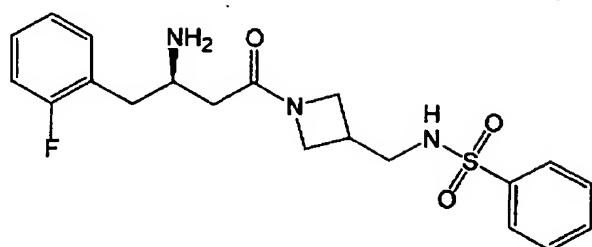
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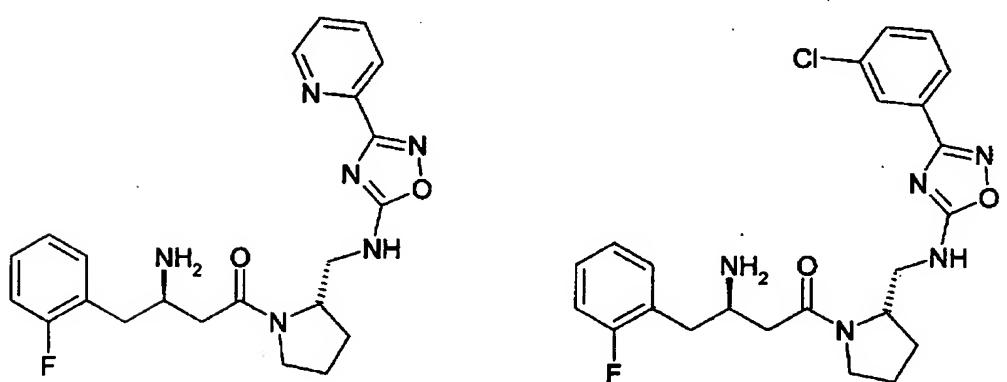
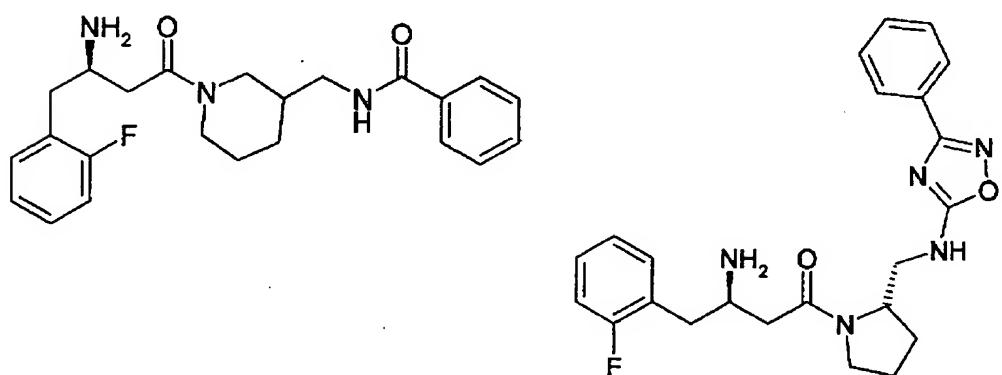
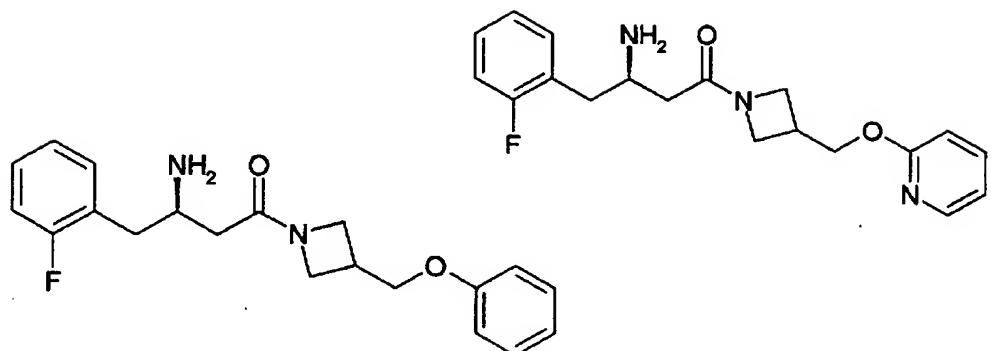
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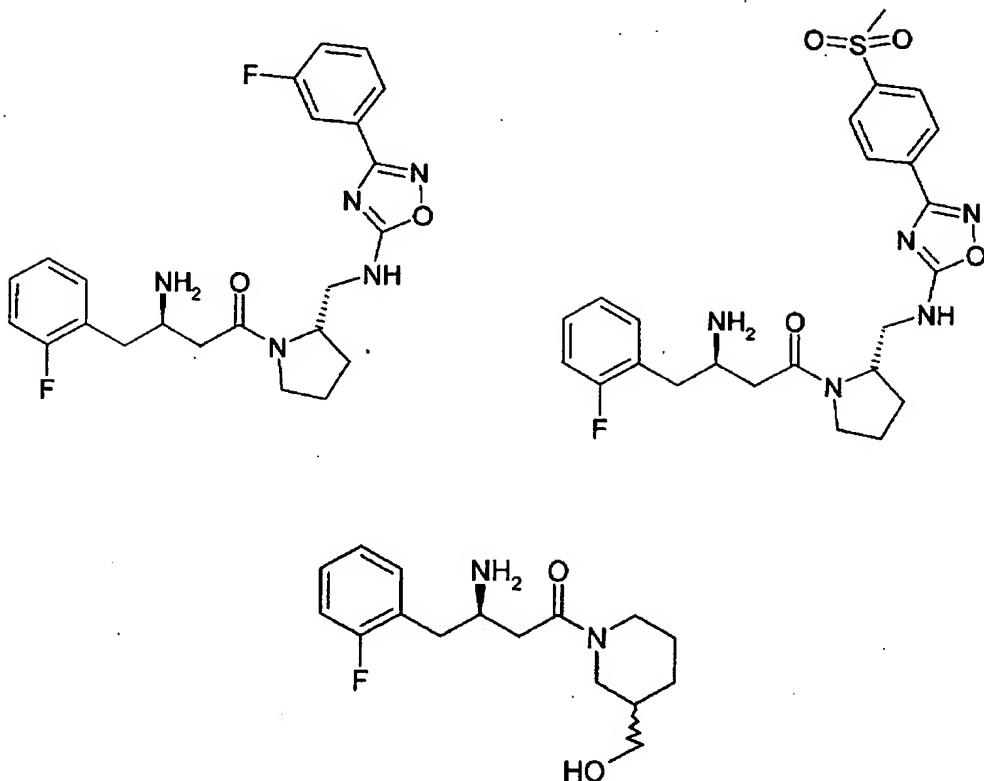
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or a pharmaceutically acceptable salt thereof.

17. (Previously presented) A prodrug compound of a compound according to claim 1.
18. (Currently amended) A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof or a prodrug thereof according to claim 1 together with a pharmaceutically acceptable carrier.
19. (Currently amended) A pharmaceutical composition according to claim 18, comprising one or more additional compounds or pharmaceutically acceptable salts thereof selected from the group consisting of another of said compound of formula (I), said pharmaceutically

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acceptable salt thereof or a prodrug thereof; another DPP-IV inhibitor; insulin sensitizers; PPAR agonists; biguanides; protein tyrosinephosphatase-IB (PTP-1B) inhibitors; insulin and insulin mimetics; sulfonylureas and other insulin secretagogues; α -glucosidase inhibitors; glucagon receptor antagonists; GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists; GIP, GIP mimetics, and GIP receptor agonists; PACAP, PACAP mimetics, and PACAP receptor agonists; cholesterol lowering agents; HMG-CoA reductase inhibitors; sequestrants; nicotinyl alcohol; nicotinic acid or a salt thereof; PPAR α agonists; PPAR α/γ dual agonists; inhibitors of cholesterol absorption; acyl CoA : cholesterol acyltransferase inhibitors; anti-oxidants; PPAR γ agonists; antiobesity compounds; an ileal bile acid transporter inhibitor; and anti-inflammatory agents.

20. (Currently amended) A compound or a pharmaceutically acceptable salt thereof or a prodrug thereof of claim 1 for use as a medicament.

21. (Currently amended) A method Use of a compound or a pharmaceutically acceptable salt thereof of claim 1 for the manufacture of a medicament for the treatment or prophylaxis of non-insulin dependent (Type II) diabetes mellitus; hyperglycemia; obesity; insulin resistance; lipid disorders; dyslipidemia; hyperlipidemia; hypertriglyceridemia; hypercholesterolemia; low HDL; high LDL; atherosclerosis; growth hormone deficiency; diseases related to the immune response; HIV infection; neutropenia; neuronal disorders; anxiety; depression; tumor metastasis; benign prostatic hypertrophy; gingivitis; hypertension; osteoporosis; diseases related to sperm motility; low glucose tolerance; insulin resistance; ist sequelae; vascular restenosis; irritable bowel syndrome; inflammatory bowel disease; including Crohn's disease and ulcerative colitis; other inflammatory conditions; pancreatitis; abdominal obesity; neurodegenerative disease; retinopathy; nephropathy; neuropathy; Syndrome X; ovarian hyperandrogenism (polycystic ovarian syndrome; Type n diabetes; or growth hormone deficiency, comprising administering to a subject in need of said treatment said compound or said pharmaceutically acceptable salt thereof or a prodrug thereof of claim 1.

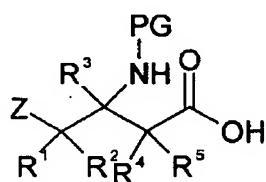
22. (Currently amended) A method to inhibit Use of a compound according to claim 1 as DPP-IV inhibitor peptidase activity comprising administering said compound or said

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pharmaceutically acceptable salt thereof or a prodrug thereof of claim 1 to a subject in an amount sufficient to inhibit DPP-IV peptidase activity.

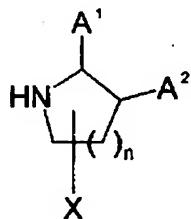
23. (Previously presented) Process for the preparation of a compound according to claim 1, comprising the steps of

- coupling of an amino-protected beta-amino acid of formula (IVa)



(IVa)

wherein PG is a protective group, with an amine of formula (III)



(III)

using standard peptide coupling conditions, reagents and protective groups;

- removing the protective group (PG).

24. (Original) A process according to claim 23, wherein the coupling reagents are 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) in combination with 1-hydroxybenzotriazole (HOEt) and a base (triethylamine or diisopropylethylamine) or O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) in the

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presence of a base and the protective group is 9-fluorenylmethoxycarbonyl or *tert*-butoxycarbonyl.

25. (Previously presented) A process according to claim 23, wherein the protective group is removed using diethylamine in dichloromethane in the case of 9-fluorenylmethoxycarbonyl or using acidic conditions in the case of *tert*-butoxycarbonyl.